Review

Clinical Cancer Research

Keratinocyte Carcinomas: Current Concepts and Future Research Priorities

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Abstract

Cutaneous squamous cell carcinoma (cSCC) and basal cell carcinoma (BCC) are keratinocyte carcinomas, the most frequently diagnosed cancers in fair-skinned populations. Ultraviolet radiation (UVR) is the main driving carcinogen for these tumors, but immunosuppression, pigmentary factors, and aging are also risk factors. Scientific discoveries have improved the understanding of the role of human papillomaviruses (HPV) in cSCC as well as the skin microbiome and a compromised immune system in the development of both cSCC and BCC. Genomic analyses have uncovered genetic risk variants, high-risk susceptibility genes, and somatic events that underlie common pathways important in keratinocyte carcinoma tumorigenesis and tumor characteristics that have enabled development of prediction models for early identification of high-risk individuals. Advances in chemoprevention in high-risk individuals and progress in targeted and immune-based treatment approaches have the potential to decrease the morbidity and mortality associated with these tumors. As the incidence and prevalence of keratinocyte carcinoma continue to increase, strategies for prevention, including effective sun-protective behavior, educational interventions, and reduction of tanning bed access and usage, are essential. Gaps in our knowledge requiring additional research to reduce the high morbidity and costs associated with keratinocyte carcinoma include better understanding of factors leading to more aggressive tumors, the roles of microbiome and HPV infection, prediction of response to therapies including immune checkpoint blockade, and how to tailor both prevention and treatment to individual risk factors and needs.

Introduction

Keratinocyte carcinoma, comprised of cutaneous squamous cell carcinoma (cSCC) and basal cell carcinoma (BCC), are the most frequently diagnosed cancers in the Western world (1, 2). Although the exact worldwide incidence of keratinocyte carcinoma is unknown, keratinocyte carcinoma represents a significant health burden in many countries. An estimated 5.4 million keratinocyte carcinomas were diagnosed in the United States in 2012, an increase from 3.5 million cases in 2006 (3, 4). In addition to significant morbidity, they are responsible for an estimated 4,000–8,700 deaths per year in the United States and cost approximately $4.8 billion annually (5, 6). In 2014, the U.S. Surgeon General launched the "Call to Action to Prevent Skin Cancer" that aimed to reduce skin cancer incidence and mortality, including that of both keratinocyte carcinomas and melanoma. Similar campaigns have been launched elsewhere, with most notable impact in Australia (7).

Molecular, epidemiologic, and clinical studies have led to greater understanding of the cellular events that occur during tumorigenesis, epidemiologic risk factors, and have provided new strategies for treatment and prevention of keratinocyte carcinomas. In this review, we will discuss similarities and differences between BCC and cSCC in terms of histopathology, risk factors, and tumor development. We also highlight advances and gaps in our knowledge and emerging therapeutic and preventative strategies needed to decrease the impact of these cancers.

Overview

cSCC comprise about 20% of keratinocyte carcinoma diagnoses. An estimated 3%–7% of patients develop metastasis, of whom more than 70% will die from disease (8–10). BCC comprise about 80% of all keratinocyte carcinomas. Despite population studies indicating that the BCC-associated mortality rate is negligible (10), BCC can in rare cases metastasize and lead to death (11). While ratios of BCC to cSCC ranging from 2 to 4:1 have been reported, recent studies based on Medicare records suggest this may be changing, with equal numbers of BCCs and cSCCs being treated (3). This may reflect the aging of the population.

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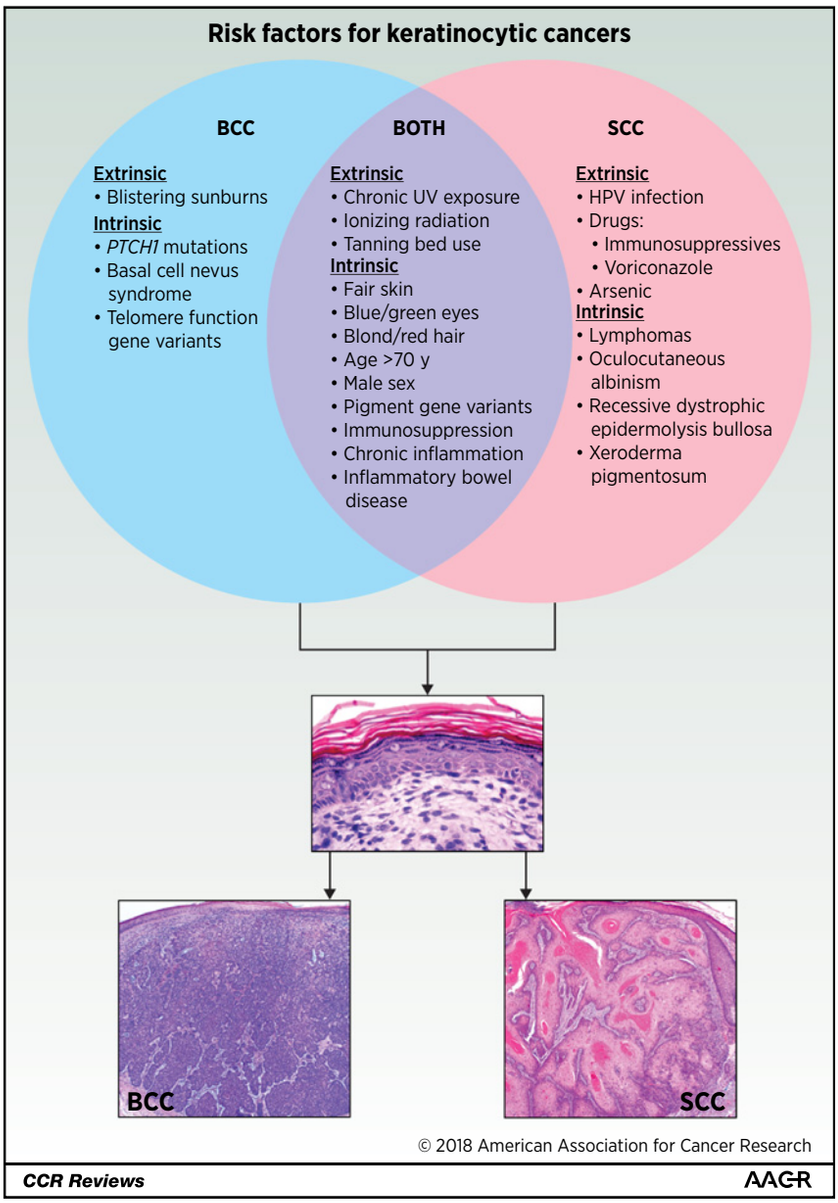

Figure 1.
Unique and shared risk factors for BCC and cSCC. Intrinsic and extrinsic risk factors for the development of BCC and cSCC are shown, including factors that are in common or unique to each tumor type. HPV, human papillomavirus; y, years.

Risk Factors

Risk factors for keratinocyte carcinoma and aggressive keratinocyte carcinoma are summarized in Fig. 1 and Table 1 and are detailed below. Prospective identification of high-risk patients and early intervention are facilitated by recognition of specific clinical and histopathologic characteristics for both BCC (12–17) and cSCC (9, 13, 18–22), so that tailored management strategies may be implemented early.

Pathophysiology

UV radiation

UV radiation is the overwhelming causative environmental carcinogen in keratinocyte carcinoma. Keratinocyte carcinomas exhibit C>T or CC>TT dinucleotide mutations at pyrimidine bases with a strong transcription strand bias. This mutational signature (signature 7) is characteristic of UV-induced mutation and common to almost all UV-associated skin cancers (23). Keratinocyte carcinomas also show a high mutational burden, far exceeding that of other cancers, although the genes mutated vary between BCCs and cSCCs (24, 25). Exome sequencing of cSCC shows highest levels of *TP53* mutations and loss-of-function *CDKN2A* mutations. Other frequent mutations are found epigenetic regulators such as *KMT2C*, *KMT2D*, *TET2*, and loss-of-function Notch pathway genes such as *NOTCH1* and *NOTCH2* (24, 25). Sequencing studies of metastatic cSCCs reveal higher mutational burden than primary tumors and have associated mutations in *KMT2C* with poorer outcome, including bone metastases (25, 26). Targeted sequencing revealed a high proportion of cSCCs (88%) contain potentially actionable but rare (<10%) genomic alterations including *PIK3CA*, *FGFR3*, *BRAF*, and *EGFR*,

Table 1. Low- and high-risk features of keratinocytic carcinomas

Features		Low risk	High risk	References
BCC				
Patient	Immune status	Immunocompetent	Immunosuppressed	12, 13
Clinical	Primary vs. recurrent[a]	Primary	Recurrent, metastatic	13–15, 17
	Anatomic location[b]	Area L and M	Area H	
	Site of prior radiotherapy[a]	No	Yes	
	Tumor dimensions[a]	Surface area: area L: <20 mm; area M: <10 mm	Surface area: area L: >20 mm; area M: >10 mm	
		Size/diameter: <5 cm	Size/diameter: >5 cm	
	Tumor circumscription[a]	Well-defined borders	Poorly defined borders	
	Involvement of named nerves[a]	Absent	Present	
Pathologic	Histologic type/growth pattern[a]	Superficial, nodular, keratotic, infundibulocystic, fibroepithelioma of Pinkus	Micronodular, infiltrative, sclerosing, morpheaform, basosquamous, metatypical/sarcomatoid	13, 14, 16, 17
	Perineural invasion[a]	Absent	Present, diameter of involved nerve $\geq$0.1 mm, multifocality, involvement of named nerves	
SCC				
Patient	Immune status[a]	Immunocompetent	Immunosuppressed	13, 18, 19, 21
	Neurologic symptoms[a]	Absent	Present	
Clinical	Primary vs. recurrent[a]	Primary	Recurrent, metastatic	9, 13, 18, 19, 21, 22
	Anatomic location[b]	Area L and M	Area H	
	Site of prior radiotherapy[a]	No	Yes	
	Site of chronic inflammation[a]	No	Yes	
	Rate of growth[a]	Slow	Rapid	
	Tumor dimensions[a]	Surface area: area L: <20 mm; area M: <10 mm	Surface area: area L: >20 mm; area M: >10 mm	
		Size/diameter: <2 cm	Size/diameter: >2 cm	
	Tumor circumscription[a]	Well-defined borders	Poorly defined borders	
	Involvement of named nerves	Absent	Present	
	Extension into osseous structures	Absent	Present	
Pathologic	Histologic grade[a]	Well or moderately differentiated (G1–2)	Poorly differentiated (G3)	9, 13, 18–22
	Histologic type/growth pattern[a]	Subtype not otherwise specified	Acantholytic (adenoid), adenosquamous, desmoplastic, spindled, metaplastic/sarcomatoid	
	Perineural invasion[a]	Absent	Present, diameter of involved nerve $\geq$ 0.1 mm, multifocality, involvement of deep dermal nerves or named nerves	
	Lymphovascular invasion[a]	Absent	Present	
	Anatomic (Clark) level[a]	I–III	IV–V	
	Tumor depth[a]	<2.0 mm	>2.0 mm	
	Lymph node metastasis	Absent	Present, size of metastasis >3.0 cm, presence of extranidal extension, involvement of contralateral lymph nodes	

[a]Features defined by the National Comprehensive Cancer Network.
[b]Human body skin is classified into three regions according to risk for aggressive keratinocyte carcinoma: area H with high risk (frontal hairline, central face, nose, eyelids, chin, ear, genitalia, hands, feet, and bald scalp); area M with moderate risk (cheeks, forehead, scalp, neck, and jawline); and area L with low risk (trunk and extremities, excluding H and M areas).

suggesting potential areas for clinical trials (27). Commonly mutated genes in BCC include those in the sonic hedgehog (SHH) signaling pathway (*PTCH1, SUFU, SMO*) as well as *TP53*. Genes mutated less frequently (8%–30%) include *MYCN, PPP6C, PTPN14,* and *RB1* (28).

Immunosuppression

Innate or acquired immunosuppression is a significant risk factor for keratinocyte carcinoma, particularly cSCC. While certain primary immunodeficiencies predispose to keratinocyte carcinoma (ref. 29; e.g., severe combined immunodeficiency, Wiskott–Aldrich syndrome, and dyskeratosis congenita), keratinocyte carcinomas are more common in acquired immunodeficiency, including immunosuppressive drug therapy (e.g., in solidorgan transplantation), immunemediated/autoimmune inflammatory diseases (IMID) such as inflammatory bowel disease (IBD), vasculitis and rheumatoid arthritis (RA), nonHodgkin lymphoma/chronic lymphocytic leukemia (NHL/CLL), and HIV infection (30).

Solid-organ transplant recipients (SOTR) are the most intensively studied iatrogenically immunosuppressed population: they have a 60- to 200-fold increased risk of cSCC, with reversal of the usual BCC to cSCC ratio, frequent occurrence of multiple tumors, and a potentially more aggressive clinical course (31–34). Age-adjusted population estimates in the United States have shown cSCC incidence ratios (IR) of 1,355/100,000 person-years

in SOTRs compared with 38/100,000 in the general population (35). Indeed, keratinocyte carcinoma in SOTR has an IR nearly five times that of all other cancers combined in the general U.S. population (National Cancer Institute; http://seer.cancer.gov/statfacts/). Significant risk factors include age at transplantation, duration of immune suppression, skin type, gender, and organ-specific factors, with greatest keratinocyte carcinoma risk seen after thoracic transplantation. In IMIDs, the risk of keratinocyte carcinoma is also significantly increased and this is in part treatment-related (36): exposure to thiopurines is associated with up to 5-fold increased risk for cSCC in IBD (36, 37) and treatment for more than 1 year also increases cSCC risk in RA (38). Other noniatrogenically immunosuppressed individuals, including those with HIV/AIDS or with hematologic malignancies such as CLL, are also at significantly increased keratinocyte carcinoma risk (39–41). In HIV, this risk is associated with long-term survival although highly active antiretroviral therapy may be protective (42). cSCC in association with CLL has poorer outcomes with increased recurrence and metastasis (41, 43).

The pathogenesis of immunosuppression-associated keratinocyte carcinoma involves a complex interplay between UVR and a number of cofactors. Innate primary and acquired immunodeficiencies are likely to result in dysregulation of tumor immune surveillance, as do immunosuppressive drugs, but the latter may also contribute by direct carcinogenic effects. For example, a recent meta-analysis of 27 studies confirmed a 1.56-fold increased risk for cSCC [95% confidence interval (CI): 1.11–2.18] in association with azathioprine (44). Thiopurines have the dual effects of causing UVA photosensitivity with consequent UVA-induced DNA damage, together with increased UVB mutagenesis through reduced repair of UVB-induced DNA damage (45, 46). A specific azathioprine signature mutation has recently been identified in cSCC (47); procarcinogenic mechanisms for the calcineurin inhibitor, cyclosporine, include reduced UV DNA damage repair (48), reduced apoptotic response to UV (49), and ATF3 induction and suppression of p53-dependent senescence (48, 50). In contrast, mTOR inhibitors are associated with reduced cSCC risk, possibly through both antiproliferative and antiangiogenic properties (34, 51–53) and the risk associated with newer immunosuppressive drugs, including tacrolimus and mycophenolate, may also be reduced, but supportive epidemiologic data are not yet established (54, 55). Voriconazole, an antifungal agent commonly used in transplantation, has direct photocarcinogenic effects (56) and is associated with significantly increased risk of aggressive cSCC (57). Other drugs used in IMIDs, including anti-TNF agents, have also been implicated in contributing to keratinocyte carcinoma risk, but data are less conclusive.

Human Papillomavirus

Patients with epidermodysplasia verruciformis (EV), a rare, autosomal-recessive disorder characterized by impaired cellular immunity, represent another unique population with markedly elevated cSCC risk. Cutaneous human papillomavirus (cuHPV) of the genus beta (βHPV) are particularly implicated in cSCC and were first identified in patients with EV, although are also common in immunocompetent individuals (58). βHPV DNA has been detected in 18%–84% of cSCCs and is three times more likely to be present in cSCCs arising among immunocompromised individuals than immunocompetent individuals (59). However, when βHPV is detected in cSCC, viral DNA is present at low copy numbers (60), and viral transcripts are absent (61). Therefore, unlike the high-risk mucosal types associated with cervical and anogenital cancers, if βHPV plays a role in keratinocyte carcinogenesis, it does so through an indirect mechanism, such as inhibition of DNA repair and/or apoptosis of UV-damaged cells (62). Multiple epidemiologic studies, incorporating both serologic and DNA-based markers of βHPV infection, have observed increased risk of cSCC associated βHPV infection (63). While these associations may simply reflect alterations in immune function that predispose individuals to both βHPV infection and cSCC, the consistent signal observed across studies underscores the need for additional research into the biology underpinning the complex interplay between UV radiation exposure, immune function, βHPV infection and keratinocyte carcinoma carcinogenesis, as βHPV vaccination could be a novel strategy for keratinocyte carcinoma prevention.

Microbiome/Infection

Chronic skin diseases with altered skin microbiota such as atopic dermatitis (64), psoriasis, and hidradenitis suppurativa (65, 66) may alter keratinocyte carcinoma development. One study identified 6-N-hydroxyaminopurine in a strain of *Staphylococcus epidermidis*, which can inhibit DNA polymerase in several human tumor cell lines, including those derived from cSCC (67). Furthermore, metagenomic analyses of the human skin microbiome revealed higher prevalence of such *S. epidermidis* strains in healthy individuals. As evidence is currently circumstantial, additional studies are needed to further explore the etiopathogenic role of the microbiome in cSCC.

Germline Genetic Risk Factors and Risk Models

Although factors including immunosuppression, age, sex, pigment, and UV exposure play critical roles in the risk of developing keratinocyte carcinoma (Fig. 1), highly-penetrant pathogenic variants and lower penetrance susceptibility variants also increase risk. Hereditary syndromes associated with increased risk of cSCC are rare; these include xeroderma pigmentosum, epidermolysis bullosa, Fanconi anemia, oculocutaneous albinism, and aging syndromes such as Werner syndrome (reviewed in https://www.cancer.gov/types/skin/hp/skin-genetics-pdq). Basal cell nevus syndrome (BCNS/Gorlin syndrome), caused by pathogenic variants in the *PTCH1* gene and more rarely *PTCH2* (68) and *SUFU* (69), is the main syndrome associated with an increased risk of BCC. Other syndromes such as Rombo, Bazex-Dupré-Christol, and xeroderma pigmentosum also show increased BCC risk (70).

Genome-wide association studies (GWAS) have identified variants (or genes) associated with increased risk for keratinocyte carcinoma and melanoma. Pathways linked to increased risk of cSCC and/or BCC in the general population include genes critical for pigment (*IRF4*, *OCA2*, *HERC2*, *TYR*, *SLC45A2*, *ASIP*, *RALY*, and *MC1R*), and HLA (*HLADQA1*; refs. 71, 72). BCC GWAS have also identified variants in telomere function genes and those important in immune regulation (72). Most of these variants show small effect sizes with typical ORs ranging from 1.15 to 1.5. Although the total number of variants associated with keratinocyte carcinoma risk is still small, there may be future benefit of using polygenic risk scores to identify individuals at elevated risk

who would then be candidates for sun-protective education, behavioral intervention, and/or increased screening (73, 74).

Associations between aberrant human leukocyte antigen (HLA) expression (75, 76), or germline class-I and II allelic variations and keratinocyte carcinoma have been controversial (77–80) and are affected by high UV exposure (81), immunosuppression (82), and HPV infection (83). Multiple variants in *HLA-DRB1* (**01*,**07*) have shown increased risk for BCC while *HLA-DRB1*04* was protective (82). *HLA-DRB1*01* also correlated with increased BCC risk and early tumor development in renal transplant recipients (84). Among immunosuppressed patients, class-I antigens *HLA-A03*, *HLA-A11*, and *HLA-B27* and class-II antigens, *HLA-DRB1*07* and *HLA-DQA1*01* correlated with increased risk cSCC (80). GWAS analyses revealed higher cSCC risk in association with *DRB1*01*, *DQA1*05:01*, and *DQA1*05:05* (85), in addition to variants in *HLA-DQB1* (72), *HLA-DQA1* (71), *HLA-DRB1* (85), and *HLA-DQA1* (85). On the other hand, HLA mismatch between recipient and graft appears to have a protective effect on keratinocyte carcinoma risk, with greater number of mismatched alleles conferring higher protective effect (S. Arron; manuscript under review). Further studies may reveal the connection between HLA Class I and II antigens and keratinocyte carcinoma development.

Prevention

Sun avoidance and sun-protective behavior such as avoiding the sun at peak hours between 11 am and 3 pm, wearing protective clothing and wide-brimmed hats, regularly applying sunscreen, and seeking shade have been shown in some studies to decrease the incidence of cSCC and may be effective for reduction of BCC (86, 87). However, consistent adherence to these guidelines, even in high-risk populations, such as SOTRs, is suboptimal (88, 89). Evidence shows that raising skin cancer awareness in high-risk populations can stimulate adoption of preventive practices (90, 91) and that specific sun-protection education in specialist dermatologic-surgery clinics for SOTRs at very high keratinocyte carcinoma risk, can bring about measurable behavior change (92). There remains a need for new studies to determine the delivery of effective education programs for sustained sun-protective behavior strategies for prevention of keratinocyte carcinomas and to develop these to the point of regular use. Chemopreventive strategies for high-risk patients are also a consideration. The few clinical trials evaluating the effectiveness of preventive agents (e.g., tretinoin, vismodegib, nicotinamide) mostly were conducted in immunocompetent populations (93–95). Oral retinoids, such as isotretinoin and acitretin, and SHH pathway inhibitor vismodegib all showed decreases in the number of BCCs in individuals with BCNS compared with placebo (94, 96, 97). Isotretinoin is associated with decreases in both BCCs and cSCCs in individuals with xeroderma pigmentosa and in SOTRs (98, 99). However, these drugs have limitations which restrict their use in the general population; for example, systemic retinoids are associated with hepatotoxicity and teratogenicity as well as xerosis, and vismodegib is associated with dysgeusia and alopecia (100). A double-blinded, randomized controlled trial of nicotinamide (vitamin B3) in patients with a history of keratinocyte carcinomas found that 500 mg nicotinamide twice-daily reduced the incidence of BCC, cSCC, and actinic keratosis compared with placebo over a 12-month period without significant side effects (93). However, there is limited evidence available for nicotinamide in OTRs in keratinocyte carcinoma prevention (101), which requires confirmation in large clinical trials.

Screening

Screening the general population for keratinocyte carcinoma via full-body skin examination is unlikely to be cost-effective in unselected populations because specificity and accuracy of clinical diagnosis is low, and the U.S. Preventive Services Task Force states that there is insufficient evidence to recommend keratinocyte carcinoma screening for the general population (102). Increased surveillance is likely to occur resulting in increased burden on health services and costs, with unclear reduction in morbidity or mortality. On the other hand, keratinocyte carcinoma screening in high-risk groups such as SOTRs may have has the potential to reduce morbidity and mortality, although there is no clear consensus on optimal screening regimens (103).

Risk models to identify individuals at highest risk for keratinocyte carcinoma include sex and pigmentation, and for SOTRs, also include pretransplant skin cancer history and age at transplant (104). Despite similarities, the different models vary in the exact factors included. The three models for SOTRs developed in small cohorts of white renal transplant recipients may not be generalizable to other populations or organ types (105–107). An ideal risk prediction tool would stratify patients based on individual factors and translate to evidence-based screening recommendations (reviewed in ref. 104). Implementation of existing skin cancer screening guidelines has been variable (108–112), likely reflecting availability of resources. A recent population-based study in Ontario, Canada observed that fewer than half of SOTRs ever saw a dermatologist, but that higher adherence to annual screening after transplantation was associated with a reduction in surgically morbid or fatal keratinocyte carcinomas (113). Economic modeling also suggests that appropriate screening and early intervention may reduce the cost of skin cancer care after transplant (114) but prospective data are needed to further justify targeted screening for reduction in keratinocyte carcinoma morbidity and associated costs.

Treatment

Both BCC and cSCC can be successfully treated by a variety of modalities and guidelines for their management have been recently published (13, 115–117). Treatment selection is often guided by patient features, such as comorbidities and preferences, tumor features, that stratify keratinocyte carcinomas into low-risk and high-risk tumors (Table 1; Fig. 1), as well as care features, such as access to the modality and associated cost (118).

Surgery remains the mainstay of treatment for invasive keratinocyte carcinoma and includes excision with postoperative margin assessment and Mohs micrographic surgery (MMS). Low-risk primary keratinocyte carcinomas are often treated with surgical excision whereas high-risk keratinocyte carcinomas are candidates for MMS. Nonsurgical destructive options include cryosurgery, electrodessication and curettage (EDC), and chemical peels. EDC is widely used for low-risk keratinocyte carcinomas in non-hair–bearing areas on the trunk and extremities, whereas chemical peels can be used to remove superficial keratinocyte carcinomas and associated sun damage. Light-based therapies, including photodynamic therapy (PDT) and lasers, utilize discrete wavelengths of light to target keratinocyte carcinomas. Cure rates depends on

Table 2. Description, comparison, efficacy, and recommended target of common keratinocyte carcinoma treatments

Treatment	Description	Advantage(s)	Disadvantage(s)	Efficacy/recurrence rate[a]	Recommended target	References
Surgery						
Excision	Standard surgical excision followed by postoperative pathologic evaluation of margins	- Lower cost than Mohs - Fast healing if surgically repaired - Allows for pathologic confirmation of tumor removal	- Normal tissue not maximally conserved - May lead to substantial deformity in some anatomic sites (eyelid, nose)	- BCC/SCC combined 5-year recurrence rate of 3.5% (CI: 1.8–5.2)	- Low-risk primary tumors - Select high-risk tumors with margin assessment	116, 117, 126
Mohs	Surgical resection with intraoperative analysis of 100% of the excised margins	- Highest cure rate - Normal tissue maximally conserved - Allows for pathologic confirmation of tumor removal	- More expensive than excision - Requires specialist to perform	- BCC/SCC combined 5-year recurrence rate of 2.1% (0.6%–3.5%)	- High-risk tumors	116, 117, 126
Destruction						
EDC	Tumor is scraped from the skin and electricity is used to destroy remaining cancer cells in the tumor bed	- Minimally invasive - Cost-effective	- Worse cosmetic outcome (atrophic scar) - Slow healing - Cannot be used for tumors invading fat	- BCC/SCC combined 5-year recurrence rate of 4.9% (CI: 2.3%–7.4%) - Recurrence rates highly location and operator dependent	- Low-risk keratinocyte carcinomas on the trunk and extremities (in nonterminal hair-bearing areas)	116, 117, 126
Cryotherapy	Uses liquid nitrogen to destroy tumor cells by freeze–thaw cycles, reducing the temperature of target tissue to −50 to −60°C	- Minimally invasive - Cost-effective - Minimizes injury to normal tissue - Simple to perform	- Potentially painful to patient - Worse cosmetic outcomes compared with other treatment options	- BCC: 0%–16.5% recurrence rate - SCC: 0.8% (CI: 0.1%–2.2%) after variable follow-up	- Low-risk tumors when more effective therapies are contraindicated	116, 117, 126–129
Chemical peels	Topical solution that causes exfoliation, removing superficial keratinocyte carcinomas	- Minimally invasive	- Potential scarring (deep peels) - Long recovery time - Can only be used for superficial tumors	- Long-term efficacy data lacking	- Superficial primary tumors	130
Light-based therapies						
PDT	Application of a photosensitizing agent [aminolevulinic acid (ALA) or methyl aminolevulinate (MAL)], which concentrates selectively in rapidly dividing cells, followed by exposure to light source, generating reactive oxygen species that destroy actively proliferating cancer cells	- Noninvasive - Selective - May be painful - Good cosmetic result	- Only recommended for superficial tumors - Treatment often not covered by insurance carriers - Requires specialized equipment - Requires training to perform - Can be costly	- BCC w/MAL: 5-year recurrence rate of 30.7% (CI: 21.5%–42.6%) - SCC with variable follow-up: recurrence rate of 26.4% (CI: 12.3% to 43.7%)	- Primary superficial, low-risk tumors	116, 117, 131, 132
Lasers	- Ablative: use of a coherent light to ablate skin cancer (CO_2 laser) - Nonablative: selectively converts light to heat inside blood vessels (pulse dye lasers), destroying tumor	- Good cosmetic outcome (nonscarring) - Ablative lasers can also treat chronic photodamaged skin (photorejuvenation)		- BCC recurrence rate after neodymium laser treatment: 3.7% after 3 months to 5-year follow-up - SCC after neodymium laser treatment: recurrence rate of 4.4% after 3 months to 5-year follow-up	- Resurfacing may be of benefit for those with multiple superficial primary tumors and severe actinic damage	133, 134

(Continued on the following page)

Table 2. Description, comparison, efficacy, and recommended target of common keratinocyte carcinoma treatments (Cont'd)

Treatment	Description	Advantage(s)	Disadvantage(s)	Efficacy/recurrence rate[a]	Recommended target	References
Radiation						
Traditional	- SXRT: uses high-energy rays such as X-rays to destroy the keratinocyte carcinoma - EBRT: uses particles (photons, electrons, or protons, most commonly electron beams) to destroy the keratinocyte carcinoma	- Suitable alternative when surgery is contraindicated - Minimally invasive	- Expensive - Must be performed with special equipment - Requires multiple office visits - Higher recurrence rate than surgery - Causes DNA damage, increasing future keratinocyte carcinoma risk	- BCC 5-year recurrence rates after SXRT: 4.2% (CI: 1.9%–6.4%) - SCC 5-year recurrence rates after SXRT: 5.8% (CI: 2.9%–8.7%) - SCC recurrence rate after EBRT: 6.4% (CI: 3.0%-11.0%)	- Low-risk tumors when surgery is not feasible or preferred - Contraindicated in genetic conditions predisposing to skin cancer (e.g., basal cell nevus syndrome, xeroderma pigmentosum) - Contraindicated in skin cancer patients with connective tissue diseases (e.g., lupus, scleroderma) - Not recommended for patients age <60 years - Need long-term data on brachytherapy	116, 117, 132, 135
Brachytherapy	Focuses X-ray radiation to the tumor with the aid of a shielded surface	- High dose of treatment to target tissue - Maximal sparing of normal tissue - Shorter treatment times	- Must be performed using special equipment - Long-term side effects include pigmentation changes, hair loss, and atrophy	- Recurrence rate varies between 0%–16.7% over a period of 9 months to 10 years		136
Topical treatment						

5-Fluorouracil	Pyrimidine analogue that disrupts DNA synthesis	- Minimally invasive
		- Multiple dosing regimens
			- Side effects include significant local skin reactions with erythema, erosions, and crust that can last longer than a month
			- Limited data regarding comparative efficacy
				- Clearance rates varied by regimen, and most studies lacked long-term follow-up. Clearance rates from systematic review:
				  - Superficial BCC: 90%
				  - SCC *in situ*: 27%–85%
					- Superficial primary BCCs; not currently recommended for cSCCs based on data available	137

Imiquimod	Stimulates the immune system through binding to toll-like receptor 7		- Imiquimod used over a large surface area can cause systemic symptoms such as the flu, fatigue, headaches, and myalgia	- Clearance rates varied by regimen, and most studies lacked long-term follow-up. Clearance rates from systematic review:
				  - Superficial BCC: 43%–100%
				  - Nodular BCC: 42%–100%
				  - Infiltrative BCC: 56%–63%
				  - SCC *in situ*: 73%–88%
				  - Invasive SCC: 71%
						137

Tazarotene	Binds to retinoid receptors, blocking the differentiation of keratinocytes			- BCC: complete response rate of 30.5% after 3 year follow-up - SCC *in situ*: pilot study showed complete response of 46.6% patients after 3–5 month follow-up		138, 139

(Continued on the following page)

Table 2. Description, comparison, efficacy, and recommended target of common keratinocyte carcinoma treatments (Cont'd)

Treatment	Description	Advantage(s)	Disadvantage(s)	Efficacy/recurrence rate[a]	Recommended target	References
Ingenol mebutate	Protein C activation			- Superficial BCC: clearance rate of 63% (5/8 patients) after 85-day follow-up - No large-scale data published on SCCs		140
Diclofenac	Cyclooxygenase inhibitor			- Superficial BCC: clearance rate of 64.3% after 8 weeks of therapy		141
Intralesional injection						
Methotrexate, 5-fluorouracil, bleomycin, or interferon	Injection of agent into keratinocyte carcinoma	- Alternative for patients in whom surgery is contraindicated	- No therapeutic guidelines - Side effects include pain, erythema, ulceration, and necrosis	- Lack of large-scale study of efficacy - From systematic review: - IFNα2a cure rate: BCC = 68% (45/66); SCC = 90% (28/31) - IFNα 2b cure rate: BCC = 76% (363/479) - IFNβ cure rate: BCC = 68% (128/202) - Fluorouracil cure rate: BCC = 96% (23/24) - Bleomycin cure rate: 100% (11/11)	- Consider for use in inoperable tumors	142
Systemic therapies						
Smoothened inhibitors	Smoothened inhibitors (vismodegib and sonidegib) hinder HH pathway activation	- Can be used for inoperable tumors or locoregional or metastatic BCC	- Adverse events: muscle spasms, weight loss, dysgeusia, alopecia, and raised creatine kinase and lipase (sonidegib) - Some BCCs develop resistance	- Median duration of response: 7.6 months - Metastatic BCC response rate: 30% (CI: 16%–48%) with follow-up until 9 months after first treatment of last enrolled patient - Locally advanced BCC: 43% (CI: 31%–56%) with follow-up until 9 months	- Metastatic BCC or locally advanced BCC, genetic syndromes that increase BCC risk	121–123, 143
EGFR inhibitors	- EGFR is expressed by >90% of SCCs - EGFR inhibitors disrupt key cellular processes - Agents used in cSCC include cetuximab, lapatinib, and panitumumab	- Can be used for inoperable tumors or locoregional or metastatic cSCC	- Side effects and systemic toxicity including acne-like rash in 78% of patients, infusions reactions, and interstitial pneumopathy	- Response rate varying from 31%–69% - SCC after panitumumab: response rate of 31% with median progression-free survival of 8 months - SCC after cetuximab: response rate of 69% (CI: 52%–84%) after 6 weeks of treatment	- Metastatic cSCCs	101, 119, 144
PD-1/PD-L1 inhibitors	- Immune checkpoint inhibition that allows T cells to attack cancer cells (e.g., nivolumab, cemiplimab, and pembrolizumab)	- Can be used for inoperable tumors or locoregional or metastatic cSCC	- Side effects: fatigue, nausea, constipation, rash, diarrhea, pleural effusion, hypercalcemia, cellulitis, and pneumonitis	- Metastatic SCC: response rate of 47% (CI: 34%–61%) after median follow-up of 7.9 months	- Locally advanced and metastatic cSCCs - Not recommended for solid organ transplant recipients	125

[a]Many of these studies are small, retrospective, and/or have potential selection biases so should be interpreted with caution.

Abbreviations: EBRT, electron beam radiotherapy; SXRT, superficial X-ray therapy.

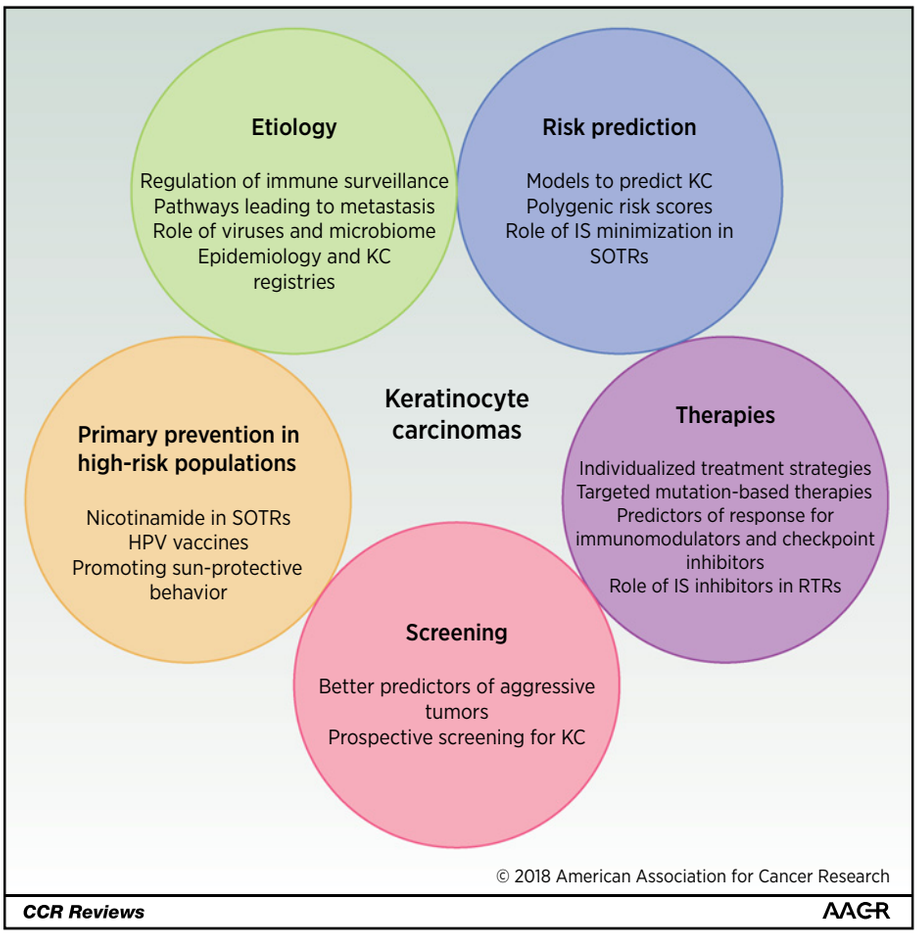

Figure 2.
Areas of research need. Some of the clinical and scientific areas in need of additional research to drive improvements in keratinocyte carcinoma (KC) understanding, prevention, treatment, and outcomes are highlighted. IS, immunosuppression; RTR, renal transplant recipients.

tumor features, choice of photosensitizing agent, and the light source. PDT can be used to treat low-risk superficial tumors in non-hair–bearing areas. Radiotherapy is recommended for non-surgical candidates and as adjuvant treatment for tumors with extensive perineural involvement but is not recommended for patients <60 years of age or those individuals with genetic syndromes predisposing to increasing skin cancer risk. Topical treatment regimens, including 5-fluorouracil, imiquimod, ingenol mebutate, diclofenac, and tazarotene, are typically reserved for superficial BCCs or SCC *in situ*. Dosing regimens and cure rates vary and are impacted by the anatomic site of the tumor, side-effect profiles, and patient compliance. Intralesional treatment with methotrexate, 5-fluorouracil, bleomycin, or interferon is an option for patients with low-risk tumors who are not surgical candidates.

For unresectable or metastatic SCC, chemotherapeutic options have included the infusion of cisplatin, 5-FU, bleomycin, and IFNα2a, with low clinical response rates (<30%; refs. 118, 119). EGFR inhibition with agents including cetuximab, lapatinib, and panitumumab has shown a moderate response but their use is limited by adverse event profiles (118, 120). Newer treatments, including targeted therapy for BCCs and immunotherapy and checkpoint inhibition therapy for cSCCs, hold some promise in the treatment of advanced and unresectable keratinocyte carcinomas. Currently available molecular therapies targeting the SHH signaling pathway often mutated in BCCs include vismodegib and sonidegib. Both agents have shown clinically meaningful response rates with 43% for locally advanced and 30% for metastatic disease (121–123). Their clinical utility is, limited by their side-effect profile, which includes muscle spasms, alopecia, taste loss, weight loss, precluding their long-term use (121–123). Inhibition of DNA repair pathways, including PARP inhibition, is a promising future therapeutic direction for SHH pathway-resistant BCCs (124). Immune checkpoint blockade has successfully treated hypermutated cancers, including SCC, enabling heightened sensitivity to effector T cells. Cemiplimab, a human mAb directed against programmed death 1, is an immune checkpoint inhibitor that has demonstrated clinical response in locally advanced (50%) and metastatic (47%) disease (125). Immune checkpoint blockade combined with other treatment modalities is a promising avenue for future systemic SCC treatment. Identification of which tumors will respond is an ongoing area of research. Table 2 describes commonly used keratinocyte carcinoma treatments and includes recommendations for use of each treatment modality (116, 117, 119–144).

Development of novel transdermal delivery systems such as nanoshells, sonophoresis, and electroporation offer promising noninvasive alternatives for the future. Despite these advances, more data are needed to make informed decisions based on individualized risk assessments guided by patient, tumor, and care factors. Appropriate therapeutic choice involves a shared decision-making plan that includes the provider and the patient.

Conclusions

With increasingly longer life expectancies, the health burden associated with keratinocyte carcinomas is likely to rise still further. Our understanding of environmental risk factors such as exposure to UV radiation, immune suppression, viruses, skin microbiome, and intrinsic risk factors such as pigmentation, aging, immune function, and genetic susceptibility variants on keratinocyte carcinoma development is growing. However, additional research is critical to build on these findings, specifically to enhance sun-protective behavior and public knowledge of the long-term harms of excessive UV exposure, to decrease the availability and use of indoor tanning, better capture, and track keratinocyte carcinoma cases via registries, improve therapies, and better predict response (Fig. 2).

Disclosure of Potential Conflicts of Interest

M.M. Asgari reports receiving commercial research grants from Pfizer and Valeant. S.T. Arron reports receiving other commercial research support (paid directly to UCSF) from Leo Pharma, SunPharma, Menlo Therapeutics, Castle Biosciences, Genentech/Roche, Pfizer, Regeneron, Eli Lilly, and PellePharm, is a consultant for Enspectra Health, Regeneron, Sanofi Genzyme, Castle Creek Pharmaceuticals, SunPharma, Pennside Partners, Biossance, Gerson Lehrman Group, and Rakuten Aspyrian, and holds ownership interest in Genentech. C.A. Harwood reports receiving other commercial research support from MEDA and Pellepharm, speakers bureau honoraria from Sanofi, and is a consultant/advisory board member for Novartis. No potential conflicts of interest were disclosed by the other authors.

Disclaimer

This content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH.

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